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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/920,332	08/02/2001	Shailaja Kasibhatla	1735.0470001/RWE/ALS	5774

26111 7590 02/26/2004

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 02/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/920,332	KASIBHATLA ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-7,9-13,28-31 and 36-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 4-7, 9-13, 28-31, and 36-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/10/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-2, 4-7, 9-13, 28-31, and 36-44 are pending.

2. The following new grounds of rejections are necessitated by the amendment filed 11/10/03.

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-2, 4-7, 9-11, 28-31, and 36-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evans *et al* (Cancer Research 54: 1596-1603, March 1994; PTO 892) in view of Porter et al (Analytical Biochemistry 123(1): 41-48, 1982; PTO 892), and US Pat No 6,342611 B1 (filed Oct 9, 1998, PTO 1449).

Evans *et al* teach a method for identifying an immunosuppressive agent such as cisplatin comprising the steps (a) obtaining a population of viable cultured active T cells such as proliferating rat thymocytes or resting T cells such as quiescent rat thymocytes having intact membranes from a cell growth medium such as PRMI 1640 under conditions conductive to growth such as incubated at 37°C, which is about 42°C, (b) incubating the reference active and resting T cells in the presence various test compound such as MP, etoposide or Cisplatin (CP) dissolved in a solvent such as dimethyl sulfoxide (DMSO) or vehicle (DMSO) alone over a predetermined period of time such as 12, 24, 36 or 48 hours (See page 1597, column 1, Materials

and Methods, isolation of Immature Rat Thymocytes, Figure 1, in particular); (c) separately adding to each culture such as Cisplatin treated, etoposide treated and vehicle control a reporter compound such as TB or acridine orange (AO) which is responsive to the caspase cascade such as cell viability or apoptosis; (d) measuring at least one measurable property such as uptake of TB and the fluorescence of acridine orange (AO) under fluorescence microscopy (visualization) for nuclear condensation, cell morphology such as membrane intactness. Cells undergoing apoptosis which is associated with caspase cascade are readily distinguishable from the number of viable cells since the latter displayed diffuse nuclear staining patterns (See page 1597, Assessment of Cell Viability, in particular) and (e) calculating the caspase activity by tabulating the number of nonviable and apoptotic cells for cisplatin treated cells (First volume) and the number of nonviable and apoptotic cells for vehicle (second volume). The reference test compound is applied to the T cells at a concentration such as 10-50μM) which is within about 1 picomolar to about 1 millimolar. The reference method further comprises adding a permeabilization enhancer such as triton X100 in PBS in combination with the reference reporter compound such as propidium iodide or permeabilized enhancer such as DMSO in combination with the reference reporter compound such as acridine orange supplied by Molecular Probes, Inc (See page 1597, column 2, Cell Cycle Analysis or Unfractionated and Purified Thymocyte Populations, Materials and Methods, in particular). The viable cultured cells in the reference method are in separate wells of a microplate such as 96-well immunoassay plates (See page 1598, column 1, first paragraph, in particular). The arbitrary ratio such as when the first ratio is greater than one as recited in claim 1 is within the teachings of Evans *et al* who teaches that following treatment with MP and ectoposite, both proliferating (active) and quiescent (resting) thymocytes exhibited a highly significant increases in the amount of apoptosis detected above control levels (See page 1600, column 2, first paragraph, in particular).

The claimed invention in claims 1 and 31 differs from the teachings of the reference only that the method wherein the reporter compound is cell permeable reporter compound comprises a caspase substrate and a fluorogenic or fluorescent moiety and calculating the ratio of caspase activity in the first volume to that of the second volume, wherein when the first ratio is greater than one, the test compound kills active T cells and is a identified as a potential immunosuppressive agent.

The claimed invention in claim 28 differs from the teachings of the reference only that the method for assaying the potency of a test compound to synergize with a known

immunosuppressant by functioning as an activator of the caspase wherein the reporter compound is cell permeable reporter compound comprises a caspase substrate and a fluorogenic or fluorescent moiety and calculating the ratio of caspase activity in the first volume to that of the second volume, wherein when the first ratio is greater than one, the test compound kills active T cells and is a identified as a potential immunosuppressive agent.

The claimed invention in claims 29 and 40 differs from the teachings of the reference only that the method wherein T cells are exposed separately to a plurality of test compounds.

The claimed invention in claims 30 and 42 differs from the teachings of the reference only that the method wherein the plurality of populations of viable cultured active T cells are in separate wells of a microtiter plate.

The claimed invention in claim 41 differs from the teachings of the reference only that the method wherein a plurality of populations of viable cultured resting T cells are exposed separately to a plurality of test compounds.

Porter et al teach a rapid fluorometric assay for measurement of any peptidase activity and the cleavage of the substrate can be monitored by the change in fluorescence intensity (See abstract, in particular). The fluorescence ratio (F(t)-F(0)/(Fc)-F(0) corresponds to the fractional hydrolysis of the dipeptides substrate where F(t), F0, and F(c) are the relative fluorescence at time t, time zero and complete hydrolysis, respectively.

The '611 patent teaches a method of drug screening for compounds that involves caspase cascade (See column 55, lines 14-15, column 55, lines 50-64, in a particular). The '611 patent teaches reporter compound such as cell permeable reporter comprising caspase substrate such as z-(VEVD)2 and fluorogenic moiety such as rhodamine 110 (See column 28, line 63, entire document, in particular). The reference method detects the changes in fluorescence either of magnitude or of wavelength within the test cell and compared to control cell which has only been contacted with the reporter compound and not with the test substance (See column 53, liens 58-64, in particular). The '611 patent teaches that the results obtained can be compared to the results obtained with the test compounds which are known to affect enzymes involved in the apoptosis cascade in cells to generate a measure of the relative effectiveness of the test substance (See paragraph bridging column 53 and column 54, in a particular). The '611 patent teaches that the advantage of whole cell high through put assay is that living cells will allow the identification of small molecule compound which either interferes or modulates protease for drug discovery and diagnostic procedure (See column 5, lines 20-38, in particular). The '611 patent teaches that the

high throughput screening assay is very versatile and made it possible to process large numbers of samples, for finding new compounds or new uses for known compounds in treating immunosuppressive disorders (See column 11, lines 58 bridging column 12, lines 1-57, in particular). The '611 patent teaches that the reference method can used to screen a cell or tissue for baseline activity of any caspase enzyme (See column 11, lines 65-67, in particular) or the test cells may be contact with one or more test substance or mixture of test substances (plurality of test compounds) in the presence of the first test compound (See column 14, liens 5-11, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the reporter compound such as the acridine orange (AO) in the method of identifying any immunosuppressive agent using active T cell as taught by Evans for the cell permeable reporter compound that comprises any caspase substrate and fluorescent moiety such as rodamine 110 as taught by the '611 patent and measuring the fluorescence ratio that correlates with caspase activity as taught by Porter et al. The fluorescent results obtained can be compared to the results obtained with the vehicle control as taught by Evan et al or the '611 patent. The fluorescent results obtained can be compared to test compounds which are known to affect enzymes involved in the apoptosis cascade in cells to generate a measure of the relative effectiveness of the test substance as taught by the '611 patent (See paragraph bridging column 53 and column 54, in a particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '611 patent teaches that the reference assay is very versatile, and the advantage of whole cell high throughput assay is that living cells will allow the identification of small molecule compound which either interferes or modulates protease for drug discovery and diagnostic procedure (See column 5, lines 20-38, in particular) or for finding new compounds or new uses for known compounds in treating immunosuppressive disorders such as Sjogren's syndrome (See column 11, lines 58 bridging column 12, lines 1-57, in particular). Porter et al teach that fluorometric assay for measurement of any peptidase activity is rapid and the fluorescence ratio (F(t)-F(0)/(Fc)-F(0) corresponds to the fractional hydrolysis of the dipeptides substrate where F(t), F0, and F(c) are the relative fluorescence at time t, time zero and complete hydrolysis, respectively. Evans *et al* teach that immunosuppressive agent such as cisplatin or etoposide mediated T cell

suppression is through activation of various caspase cascade and cell death is readily distinguishable by reporter compound such as fluorescence of acridine orange (AO) (See page 1597, Assessment of Cell Viability, in particular). It is within the purview of one ordinary skill in the fluorogenic peptide chemistry art to compare the test compound with the control by measuring the change in relative florescent intensity since the fluorescence ratio (F(t)-F(0)/(Fc)-F(0) corresponds to the fractional hydrolysis of the substrate where F(t), F0, and F(c) are the relative fluorescence at time t, time zero and complete hydrolysis as taught by Porter et al. The greater the fluorescence ratio of the test compound (first volume) as compared to the fluorescence ratio of the control (second volume), the more potent the immunosuppressive agent. The recitation of plurality of viable cultured cells are in separate wells of a mircotiter plate is within the purview of one ordinary skill in the art at the time the invention was made to put plurality of viable culture either activated or resting T cells in separate wells of a 96-wells microtiter plate as taught by the Evan et al (See page 1598, column 1, 1st paragraph, in particular).

Applicants' arguments filed 11/10/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) claims 1, 28 and 31 have been amended to recite cell permeable reporter compound wherein the compound comprises a caspase substrate, and a fluorogenic or fluorescent moiety and wherein one of measurable property is a change in fluorescence. (2) The method described by Evans et al employs acridine orange (AO) or trypan blue and neither of these compounds are caspase substrate which undergo hydrolysis in the presence of a caspase protease. (3) There is no suggestion or motivation to modify or combine the teachings of the references to arrive at the claimed invention. (4) Even if there were a proper suggestion or motivation to combining these references, none of the references teach or suggest calculating a first ratio and identifying potential immunosuppressive agents as recited in part (g) of claim 1.

In response, the '611 patent teaches a method of drug screening for compounds that involves caspase cascade (See column 55, lines 14-15, column 55, lines 50-64, in a particular). The '611 patent teaches reporter compound such as cell permeable reporter comprising caspase substrate such as z-(VEVD)2 and fluorogenic moiety such as rhodamine 110 (See column 28, line 63, entire document, claims of '611 patent, in particular). The reference method detects the changes in fluorescence either of magnitude or of wavelength within the test cell and compared to control cell which has only been contacted with the reporter compound and not with the test

substance (See column 53, liens 58-64, in particular). The '611 patent teaches that the results obtained can be compared to the results obtained with the test compounds which are known to affect enzymes involved in the apoptosis cascade in cells to generate a measure of the relative effectiveness of the test substance (See paragraph bridging column 53 and column 54, in a particular). The '611 patent teaches that the advantage of whole cell high through put assay is that the use of living cells will allow the identification of small molecule compound which either interferes or modulates protease for drug discovery and diagnostic procedure (See column 5, lines 20-38, in particular). The '611 patent teaches that the high throughput screening assay is very versatile and made it possible to process large numbers of samples, for finding new compounds or new uses for known compounds in treating immunosuppressive disorders such as Sjogren's syndrome (See column 11, lines 58 bridging column 12, lines 1-57, in particular). The '611 patent teaches that the reference method can used to screen a cell or tissue for baseline activity of any caspase enzyme (See column 11, lines 65-67, in particular) or the test cells may be contact with one or more test substance or mixture of test substances (plurality of test compounds) in the presence of the first test compounds (See column 14, liens 5-11, in particular). The motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combine for their common known purpose. Section MPEP 2144.07.

In response to applicant's arguments that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992). In this case the teachings of Evans pertaining to the method of identifying immunosuppressive agent using reporter compound such as acridine orange to assess cell viability associated with activation of caspase cascade. However, the reporter compound used by Evan is not caspase specific as pointed out by Applicant and the amendment to claims 1, 28 and 31. The teachings of the '611 patent indicate the success in high throughput screening of drug using reporter compound such as cell permeable reporter comprising caspase specific substrate such as z-(VEVD)2 and fluorogenic moiety such as rhodamine 110 (See column 28, line 63, entire document, claims of '611 patent, in particular). The advantage of whole cell high through put assay is that living cells will allow the

identification of small molecule compound which either interferes or modulates protease for drug discovery and diagnostic procedure (See column 5, lines 20-38, in particular). The '611 patent teaches that the high throughput screening assay is very versatile and made it possible to process large numbers of samples, for finding new compounds or new uses for known compounds in treating immunosuppressive disorders such as Sjogren's syndrome (See column 11, lines 58 bridging column 12, lines 1-57, in particular). Zeher *et al* teach that activated T cells obtained from tissue of a patient afflicted with immunopathological symptoms such as primary Sjogren's syndrome are susceptible to apoptosis induced by various anti-CD3, anti-CD95 monoclonal antibodies and ionophore treatment. Zeher *et al* further teach that there is a positive correlation between the increased susceptibility to apoptosis of peripheral CD4+ T cells and activity of disease from patient with Sjogren's syndrome compared with resting T cells from healthy tissue that is not afflicted with the immunopathological symptoms (See abstract, in particular). Wesselborg *et al* teach that anti-CD3 TcR monoclonal antibodies trigger apoptosis in activated but not resting mature peripheral T cells (See abstract, in particular). The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983), See MPEP 2144.

In response to applicant's argument that none of the references teach or suggest calculating a first ratio and identifying potential immunosuppressive agents as recited in part (g) of claim 1, it is within the purview of one ordinary skill in the fluorogenic peptide chemistry art to compare the test compound with the control as taught by Evans et al or the '611 patent by measuring the change in relative florescent intensity as taught by the '611 patent or by measuring the fluorescence ratio (F(t)-F(0)/(Fc)-F(0) corresponds to the fractional hydrolysis of the substrate where F(t), F0, and F(c) are the relative fluorescence at time t, time zero and complete hydrolysis as taught by Porter et al. The greater the fluorescence ratio of the test compound (first volume) as compared to the fluorescence ratio of the control (second volume), the more potent is the immunosuppressive agent.

6. Claims 12-13, 43 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evans *et al* (Cancer Research 54: 1596-1603, March 1994; PTO 892) in view of Porter et al (Analytical Biochemistry 123(1): 41-48, 1982; PTO 892), and US Pat No 6,342611 B1 (filed Oct 9, 1998, PTO 1449). as applied to claims 1-2, 4-7, 9-11, 28-31, and 36-42 mentioned above and further in view of Wesselborg *et al* (Eur J Immunol 23(10): 2707-10, Oct 1993; PTO 892).

The combined teachings of Evans et al, Porter *et al*, and the '611 patent have been discussed supra.

The claimed invention in claims 12 and 43 differs from the teachings of the reference only that the method wherein the active T cells are obtained by adding to T cells antibodies to the T cell receptor, Concanavalin A or Phytohaemagglutinin.

The claimed invention in claims 13 and 44 differs from the teachings of the reference only that the method wherein the active T cells are obtained from tissue of a patient afflicted with one or more immunopathological symptoms and wherein said resting T cells are from healthy tissue that is not afflicted with the immunopathological symptoms.

Wesselborg *et al* teach that anti-CD3 TcR monoclonal antibodies trigger apoptosis in activated but not resting mature peripheral T cells (See abstract, in particular).

Zeher *et al* teach that activated T cells obtained from tissue of a patient afflicted with immunopathological symptoms such as primary Sjogren's syndrome are susceptible to apoptosis induced by various anti-CD3, anti-CD95 monoclonal antibodies and ionophore treatment. Zeher *et al* further teach that there is a positive correlation between the increased susceptibility to apoptosis of peripheral CD4+ T cells and activity of disease from patient with Sjogren's syndrome compared with resting T cells from healthy tissue that is not afflicted with the immunopathological symptoms (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use T cells from tissue from patient afflicted with any one or more immunopathological symptoms and T cells from healthy tissue as control as taught by Zeher *et al* and activate the T cells by adding anti-CD3 antibodies to the T cell receptor as taught by Wesselborg *et al* for a method of identifying immunosuppressive agent by detecting caspase activity using cell permeable reporter compound that comprises caspase peptide substrate and florescent moiety such as rhodamine 110 as taught by the '611 patent and detecting T cell activation as taught by Even et al. From the combined teachings of the references, it is apparent

that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Wesselborg *et al* teach that anti-CD3 TcR monoclonal antibodies trigger apoptosis in activated but not resting mature peripheral T cells (See abstract, in particular). Zeher *et al* teach that there is a positive correlation between the increased susceptibility to apoptosis of peripheral CD4+ T cells and activity of disease from patient with Sjogren's syndrome compared with resting T cells from healthy tissue that is not afflicted with the immunopathological symptoms (See abstract, in particular). The '611 patent teaches that the reference assay is very versatile, and the advantage of whole cell high throughput assay are that living cells will allow the identification of small molecule compound which either interferes or modulates protease for drug discovery and diagnostic procedure (See column 5, lines 20-38, in particular).

Porter et al teach that fluorometric assay for measurement of any peptidase activity is rapid and the fluorescence ratio (F(t)-F(0)/(Fc)-F(0) corresponds to the fractional hydrolysis of the dipeptides substrate where F(t), F0, and F(c) are the relative fluorescence at time t, time zero and complete hydrolysis, respectively. Evans *et al* teach that immunosuppressive agent such as cisplatin or etoposide mediated T cell suppression is through activation of various caspase cascade and cell death is readily distinguishable by reporter compound such as fluorescence of acridine orange (AO) (See page 1597, Assessment of Cell Viability, in particular).

Applicants' arguments filed 11/10/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) claims 1, 28 and 31 have been amended to recite cell permeable reporter compound wherein the compound comprises a caspase substrate, and a fluorogenic or fluorescent moiety and wherein one of measurable property is a change in fluorescence. (2) The method described by Evans et al employs acridine orange (AO) or trypan blue and neither of these compounds are caspase substrate which undergo hydrolysis in the presence of a caspase protease. (3) There is no suggestion or motivation to modify or combine the teachings of the references to arrive at the claimed invention. (4) Even if there were a proper suggestion or motivation to combining these references, none of the references teach or suggest calculating a first ratio and identifying potential immunosuppressive agents as recited in part (g) of claim 1.

In response, the '611 patent teaches a method of drug screening for compounds that involves caspase cascade (See column 55, lines 14-15, column 55, lines 50-64, in a particular). The '611 patent teaches reporter compound such as cell permeable reporter comprising caspase substrate such as z-(VEVD)2 and fluorogenic moiety such as rhodamine 110 (See column 28, line 63, entire document, claims of '611 patent, in particular). The reference method detects the changes in fluorescence either of magnitude or of wavelength within the test cell and compared to control cell which has only been contacted with the reporter compound and not with the test substance (See column 53, liens 58-64, in particular). The '611 patent teaches that the results obtained can be compared to the results obtained with the test compounds which are known to affect enzymes involved in the apoptosis cascade in cells to generate a measure of the relative effectiveness of the test substance (See paragraph bridging column 53 and column 54, in a particular). The '611 patent teaches that the advantage of whole cell high through put assay is that the use of living cells will allow the identification of small molecule compound which either interferes or modulates protease for drug discovery and diagnostic procedure (See column 5, lines 20-38, in particular). The '611 patent teaches that the high throughput screening assay is very versatile and made it possible to process large numbers of samples, for finding new compounds or new uses for known compounds in treating immunosuppressive disorders (See column 11, lines 58 bridging column 12, lines 1-57, in particular). The '611 patent teaches that the reference method can used to screen a cell or tissue for baseline activity of any caspase enzyme (See column 11, lines 65-67, in particular) or the test cells may be contact with one or more test substance or mixture of test substances (plurality of test compounds) in the presence of the first test compounds (See column 14, liens 5-11, in particular). The motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combine for their common known purpose. Section MPEP 2144.07.

In response to applicant's arguments that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992). In this case the teachings of Evans pertaining to the method of identifying immunosuppressive agent using reporter compound such as acridine orange to assess cell viability associated with activation of caspase cascade.

However, the reporter compound used by Evan is not caspase specific as pointed out by Applicant and the amendment to claims 1, 28 and 31. The teachings of the '611 patent indicate the success in high throughput screening of drug using reporter compound such as cell permeable reporter comprising caspase specific substrate such as z-(VEVD)2 and fluorogenic moiety such as rhodamine 110 (See column 28, line 63, entire document, claims of '611 patent, in particular). The advantage of whole cell high through put assay is that living cells will allow the identification of small molecule compound which either interferes or modulates protease for drug discovery and diagnostic procedure (See column 5, lines 20-38, in particular). The '611 patent teaches that the high throughput screening assay is very versatile and made it possible to process large numbers of samples, for finding new compounds or new uses for known compounds in treating immunosuppressive disorders such as Sjogren's syndrome (See column 11, lines 58 bridging column 12, lines 1-57, in particular). Zeher *et al* teach that activated T cells obtained from tissue of a patient afflicted with immunopathological symptoms such as primary Sjogren's syndrome are susceptible to apoptosis induced by various anti-CD3, anti-CD95 monoclonal antibodies and ionophore treatment. Zeher *et al* further teach that there is a positive correlation between the increased susceptibility to apoptosis of peripheral CD4+ T cells and activity of disease from patient with Sjogren's syndrome compared with resting T cells from healthy tissue that is not afflicted with the immunopathological symptoms (See abstract, in particular). Wesselborg *et al* teach that anti-CD3 TcR monoclonal antibodies trigger apoptosis in activated but not resting mature peripheral T cells (See abstract, in particular). The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983), See MPEP 2144.

In response to applicant's argument that none of the references teach or suggest calculating a first ratio and identifying potential immunosuppressive agents as recited in part (g) of claim 1, it is within the purview of one ordinary skill in the fluorogenic peptide chemistry art to compare the test compound with the control as taught by Evans et al or the '611 patent by measuring the change in relative florescent intensity as taught by the '611 patent or by measuring the fluorescence ratio (F(t)-F(0)/(Fc)-F(0) corresponds to the fractional hydrolysis of the substrate where F(t), F0, and F(c) are the relative fluorescence at time t, time zero and complete hydrolysis as taught by Porter et al. The greater the fluorescence ratio of the test compound (first volume) as

compared to the fluorescence ratio of the control (second volume), the more potent is the immunosuppressive agent.

7. No claim is allowed.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.

10. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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